



High-Grade Ectopic Pituitary Adenoma within the Cerebellopontine Angle: A Case Report

Cassidy Anderson¹ Aishwarya Sriram² Abigail Funari³ Kevin Hsu⁴ Raquel Yokoda⁵
Isabella Pecorari³ Isabella Flaquer³ Nadeem Akbar¹ Patrick Colley¹ Geoffrey Basson²
Howard S. Moskowitz¹ Vijay Agarwal³

¹Department of Otorhinolaryngology – Head and Neck Surgery, Albert Einstein College of Medicine, Bronx, New York, United States

²Department of Ophthalmology, Albert Einstein College of Medicine, Bronx, New York, United States

³Department of Neurological Surgery, Albert Einstein College of Medicine, Bronx, New York, United States

⁴Department of Radiology, Albert Einstein College of Medicine, Lower Level, Bronx, New York, United States

⁵Department of Pathology, Albert Einstein College of Medicine, Lower Level, Bronx, New York, United States

Address for correspondence Vijay Agarwal, MD, Department of Neurological Surgery, Albert Einstein College of Medicine, 3316 Rochambeau Ave, Bronx, NY 10467, United States (e-mail: vagarwal@montefiore.org).

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Abstract

Ectopic pituitary tumors are neoplasms with no connection to the pituitary gland and are commonly deposited in other areas of the anterior skull base. A 32-year-old woman presented with a 3-month history of right-sided facial weakness, sensorineural hearing loss, diplopia, and severe headaches. Physical examination revealed a mid-dilated sluggishly reactive right pupil with slight limitation in all gazes, as well as right-sided orbicularis weakness, lagophthalmos, and decreased facial sensation. A magnetic resonance imaging (MRI) of the head without contrast revealed a $3.7 \times 1.8 \times 2.6$ cm mildly enhancing mass in the right internal acoustic meatus and along the petrous ridge. The case was brought before the institution's tumor board, where concern for higher grade pathology, such as hemangiopericytoma, was discussed. Per patient preference, surgical biopsy of the tumor was performed. Immunohistochemical staining revealed a World Health Organization (WHO) grade II neuroendocrine tumor, with cells staining positive for synaptophysin, chromogranin, and CD56, with a Ki-67 index of 8%. In addition to the ectopic location, this pituitary tumor was noted to be aggressive in nature based on its high Ki-67 index. Surgical excision and radiologic therapy of tumors involving the CPA are appropriate treatments in most cases.

Keywords

- ▶ ectopic pituitary tumor
- ▶ neuroendocrine tumor
- ▶ cerebellopontine angle tumor

Introduction

Pituitary adenomas, more recently defined as pituitary neuroendocrine tumors (PitNETs), originate in the anterior pituitary lobe and are the most common type of tumor

within the sella, accounting for 10 to 15% of all intracranial lesions.^{1–3} The prevalence of PitNETs ranges from 1 in 865 to 1 in 2,688 adults, with approximately half being microadenomas and the remaining macroadenomas.⁴ Due to the

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wide functionality of the pituitary gland, the clinical presentation of a PitNET varies depending upon the characteristics of the tumor and disruption of the normal pituitary gland. In hormone-secreting PitNETs, patients present with syndromes indicative of the hormone in excess.^{1,2} In nonsecreting PitNETs, the size of the tumor will cause gradual visual defects, hypopituitarism due to gland compression, and, in some cases, hyperprolactinemia. Large PitNETs may present with signs of increased intracranial pressure and hydrocephalus.² Analysis of functional PitNET genotypes reveals that these tumors are monoclonal with clonal expansion occurring from a somatic cell mutation.^{1,5} Secreting PitNETs are classified based upon the type of hormone secreted in excess, such as corticotrophs (adrenocorticotrophic hormone [ACTH] hypersecretion), somatotrophs (growth hormone [GH] hypersecretion), mammosomatotrophs (GH and prolactin [PRL] hypersecretion), thyrotrophs (thyroid-stimulating hormone [TSH] hypersecretion), lactotrophs (PRL hypersecretion), and gonadotrophs (follicle-stimulating hormone/luteinizing hormone [FSH/LH] hypersecretion).^{1,6} Null cell PitNETs are nonsecreting pituitary tumors.⁶ Prolactinomas (40–57% of all adenomas) are the most prevalent subtype of PitNET, followed by nonfunctioning adenomas (28–37%), GH-secreting adenomas (11–13%), and ACTH-secreting adenomas (1–2%). Rare PitNETs include gonadotrophic and thyrotrophic adenomas. PitNETs are also categorized by size, with microadenomas defined as having a diameter less than 10 mm and macroadenomas having a diameter greater than 10 mm. Microadenomas are more common than macroadenomas.¹ Because PitNETs may be hormone secreting, management of such tumors involves multidisciplinary cooperation of surgical, medical, and radiotherapeutic management.⁷

In addition to the sellar region, the cerebellopontine angle (CPA) is another common anatomic location for tumor formation and is the most common site for posterior fossa tumors. The CPA is defined as the cisternal space surrounded by tentorium in the posterior fossa with lateral borders formed by the petrous portion of the temporal bone, medial borders formed by the cerebellum and pons, and inferior border by the cranial nerves (CNs) IX, X, and XI.^{8,9} CPA tumors account for 5 to 10% of all intracranial tumors, and acoustic neuromas (i.e., vestibular schwannomas) originating from CN VIII are the most common (80%) type of CPA tumor.^{8,10} Other less common CPA tumor types include meningiomas, epidermoid and dermoid cysts, and non-acoustic schwannomas.^{8,9} Clinical presentation is most associated with hearing deficits due to anatomic origin.¹¹ In advanced tumors, patients may present with ipsilateral hearing loss, hydrocephalus, hypesthesia, and brainstem compression ultimately leading to death. However, modern imaging and operative advancements have made tumors in this area easier to diagnose and treat.⁸ Surgical intervention is indicated in cases of tumor growth in patients with low surgical risk (i.e., young age) and decreased quality of life that will be ameliorated with intervention.¹¹ The retrosigmoid transmeatal approach is utilized with favorable outcomes with experienced surgeons.^{11,12} The retrosigmoid

approach was classically associated with a postoperative cerebrospinal fluid (CSF) leak rate of 2 to 10% potentially due to the pneumatization of the petrous apex air cells; however, reconstructive techniques such as fat obliteration, cranioplasty, and eustachian tube packing have reduced the incidence of such CSF leakage complications.¹³

PitNETs that have no direct connection to the normal pituitary gland and reside outside the sella turcica are called ectopic PitNETs.^{14,15} Shuman et al reviewed 85 cases of ectopic PitNETs in which 85% were functional, with ACTH-secreting tumors being the most common, followed by PRL-, GH-, and TSH-secreting tumors, respectively.^{14,16} Ectopic PitNETs are more likely to be functional compared with typical PitNETs. Clinical presentation corresponds with the anatomic location of the tumor, as well as hormonal excess, if secretory. The most common locations for ectopic PitNETs are the sphenoid sinus, clivus, suprasellar space, nasopharynx, and cavernous sinus.¹⁶ Ectopic PitNETs are speculated to occur during anterior pituitary development. As Rathke's pouch, an outgrowth of oropharynx ectoderm, invaginates during the fourth week of gestation, the pituitary tissue will begin travelling through the craniopharyngeal canal to the sphenoid sinus and eventually contact the neurohypophysis. Ectopic PitNETs may arise from remnant tissue depositing inappropriately under respiratory epithelium along this embryonal path.¹⁴ Although PitNETs are histologically benign, ectopic PitNETs have more invasive characteristics, including tumor seeding, necrotic centers, and bone invasion.¹⁶ The first-line treatment for ectopic PitNETs is surgical resection.^{17,18}

Ectopic PitNETs have been documented to occur in various intracranial spaces as aforementioned. However, an ectopic PitNET in the CPA has been reported only once previously, to our knowledge. Here, we present a case of an ectopic PitNET in the CPA, which was determined to be World Health Organization (WHO) grade II.

Case Presentation

A 32-year-old woman presented to the emergency department with 3 months of right facial weakness, numbness, and tingling, as well as right sensorineural hearing loss, altered taste and smell, headaches, and dizziness. She also noted horizontal and vertical diplopia on right gaze and up gaze, respectively. The symptoms were noted to have progressed over time. She had no pertinent medical, surgical, or family history.

Upon examination, she was found to have right-sided orbicularis weakness with lagophthalmos, as well as decreased facial sensation on the right side. Her vision in the right eye was 20/100 with pinhole to 20/60, and her vision in the left eye was 20/25. The right pupil was 5 mm and sluggish, and the left pupil was 3 mm and briskly reactive. There was no relative afferent pupillary defect. Extraocular movements were full in the left eye, but in the right eye she had –1 limitation in up gaze with –0.5 limitation in all other directions. The remainder of the anterior exam and dilated fundus exam were unremarkable.

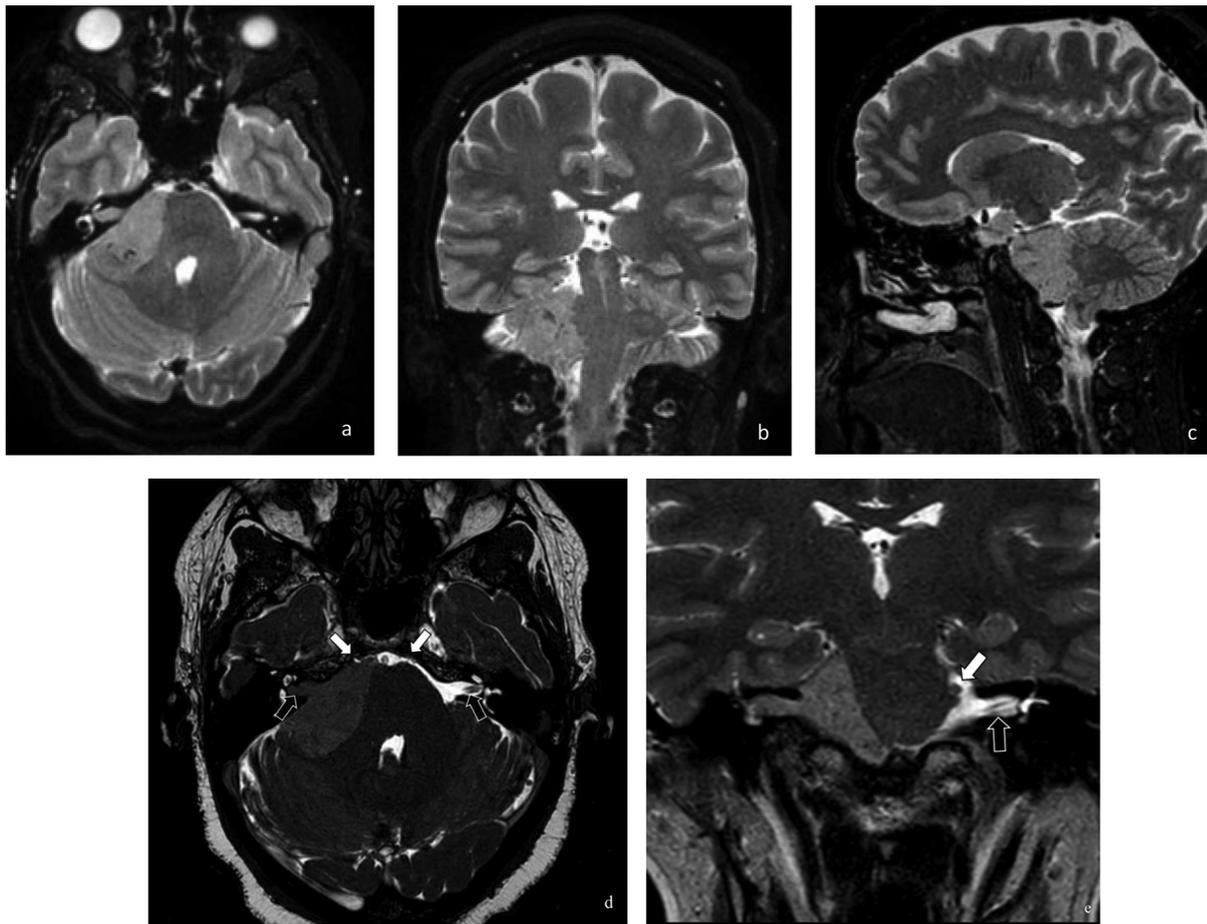


Fig. 1 Axial (a), coronal (b), and sagittal (c) T2-weighted images centered on the cerebellopontine angle demonstrate a homogeneous extra-axial mass with internal vascularity with mass effect on the pons, middle cerebellar peduncle, and cerebellum. The mass occupies the expected location of cranial nerves V,VI,VII,VIII. (d). Balanced Fast Field Echo (FFE) sequence (a sequence that allows detailed visualization of the cranial nerves in the posterior fossa) demonstrates expected locations of CN VI in Dorello's canal (*white arrow*) and CN VII and CN VIII (*black arrow*). There is a large mass within the right cerebellopontine angle extending into the right internal auditory canal and occupying the prepontine cistern along the expected course of the right CN VI. Visualization of the right-sided cranial nerves is obscured by the mass. There is mass effect on the pons and middle cerebellar peduncle with partial effacement of the fourth ventricle. (e) Coronal T2-weighted image at the level of the internal acoustic meatus demonstrates normal left-sided CN V (*white arrow*) and CN VII and CN VIII (*black arrow*). These spaces are occupied by the mass on the right and obscure visualization of the cranial nerves.

A magnetic resonance imaging (MRI) of the head with and without contrast revealed a mildly heterogeneously enhancing mass measuring $3.7 \times 1.8 \times 2.6$ cm (anteroposterior \times craniocaudal \times transverse) in the right CPA cistern and internal acoustic meatus, directly involving and encasing CNs V, VI, VII, VIII, IX, X, and XI (**Fig. 1a–e**). The lesion was isointense to gray matter on T1- and T2-weighted sequences with internal vascularity. The tumor exerted mass effect upon the cerebellum, pons, and medulla. It extended anteriorly to the prepontine cistern, bordering the basilar artery. The right vertebral artery was just inferior to the mass. No edema, midline shift, hydrocephalus, distant seeding, or bony changes were noted. There was no extension into the cavernous sinus, sella, middle or inner ear, or jugular bulb.

At this point, the differential diagnosis included vestibular schwannoma or meningioma. For diagnostic certainty, a biopsy via minimally invasive right-sided infratemporal, postauricular approach to the middle and posterior cranial fossa was performed 2 months after initial presentation. A

biopsy was performed as opposed to a more aggressive resection due to patient preference to avoid any further long-term neurological deficits after an in-depth informed consent discussion. The tumor biopsy was successfully performed without complications. The patient remained in the hospital for 1 day before being discharged uneventfully. Postoperatively, the patient was noted to have temporary facial weakness (House–Brackmann score of 2) with sensory intact in all trigeminal distributions. Her right-sided sensorineural hearing loss remained along with her gaze restrictions and diplopia, all stable to baseline.

Upon pathologic inspection, the tumor was determined to be a neuroendocrine tumor, WHO grade II, with a higher Ki-67 index of 8%. The cells featured round to irregularly shaped nuclei with small amounts of cell cytoplasm. A few mitotic figures were noted. Immunohistochemical stains showed neoplastic cells were positive for synaptophysin, chromogranin, and CD56, and immunohistochemically negative for AE1/3, CAM5.2, CK7, EMA, p63, S-100, desmin, myogenin, CD99, p53, LH, FSH, GH, PRL, ACTH, and TSH (**Fig. 2a–f**).

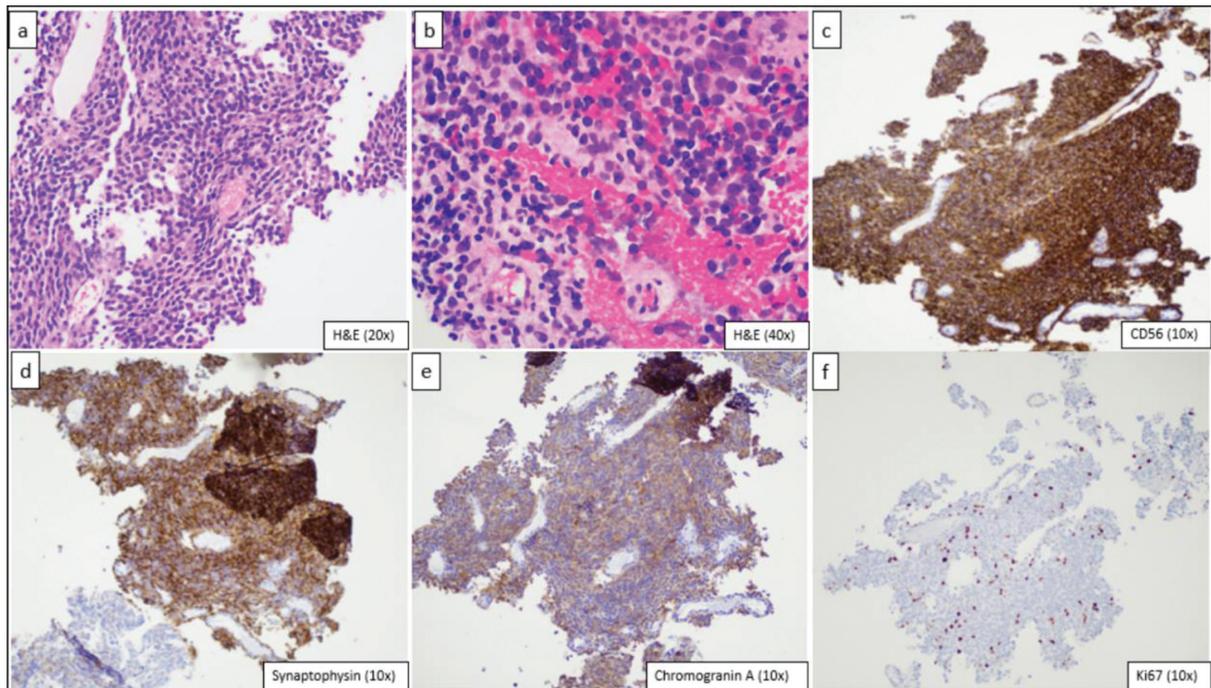


Fig. 2 (a) Hematoxylin and eosin (H&E) ($\times 20$) shows a uniform, small, bland tumor cells some with plasmacytoid appearance. (b) H&E ($\times 40$), nuclear molding with sparse areas of background necrosis, fine granular chromatin with inconspicuous nucleoli and few mitotic figures, few apoptotic bodies and vascular infiltration. (c) CD56 strong diffusely positive. (d) Synaptophysin strong diffusely positive. (e) Chromogranin A strong diffusely positive. (f) Ki67 8%, which categorizes a grade 2 (3–20% Ki67 index).

Because of the pathologic findings, it was unclear if the tumor was a primary lesion within the CPA or a metastatic tumor from an occult site. Subsequent imaging series including computed tomography (CT) of the chest, abdomen, and pelvis with and without contrast and MRI of the brain and sella were unremarkable. Positron emission tomography (PET) scan revealed greater uptake in the left lower pole of the thyroid and mild uptake among small lymph nodes suggesting benign reactive change (\rightarrow Fig. 3a, b). Ultrasound of the thyroid was notable for two nodules with high Thyroid Imaging Reporting and Data System (TIRADS) scores, for which the patient is scheduled to undergo fine needle aspiration biopsy. In line with the patient's preference, radiation therapy was then planned. Proton therapy was used to treat the right CPA tumor

and minimize dose to surrounding neural structures. A total dose of 50.4 to 60 Gy in 28 to 30 fractions was delivered.

At postoperative week 3, the patient reported an improvement in headaches with stable hearing loss and facial weakness. Physical examination revealed continued right sensorineural hearing loss and diplopia on right gaze and up gaze. Facial weakness and decreased facial sensation improved. The facial weakness improved to full strength (HB1) on long-term follow-up.

Discussion

In 2017, the International Pituitary Pathology Club moved to redefine pituitary adenomas as PitNETs due to their

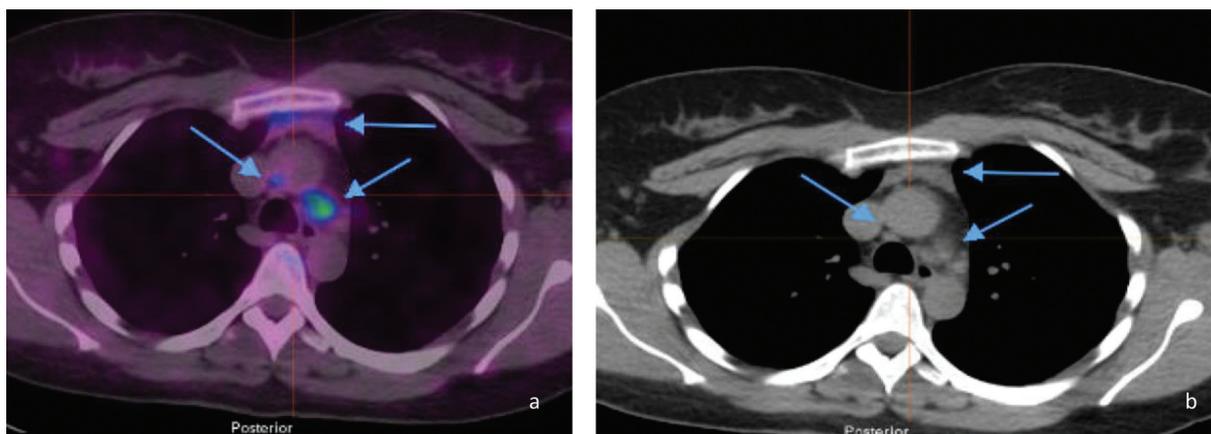


Fig. 3 (a) Nuclear Medicine (NM) gallium 68 PET/CT scan showing site of greater uptake in the left lower lobe (bottom right arrow) of the thyroid gland that corresponds to a low-density site on the CT (b) (bottom right arrow).

heterogenous nature and ability to invade adjacent structures.^{19–22} PitNETs are categorized by expanded tumor cell type. PitNETs can be descendants of lactotrophs, gonadotrophs, somatotrophs, corticotrophs, or rarely thyrotrophs. PitNETs are functional or nonfunctional according to secretion of respective anterior pituitary hormone causing endocrine disease or lack thereof.²³ Neuroendocrine tumors are broadly classified as tumors that arise from cells within the endocrine system. These tumors tend to be sporadic but can be associated with syndromes including multiple endocrine neoplasia types 1 and 2, von Hippel–Lindau disease, neurofibromatosis, and tuberous sclerosis complex. Neuroendocrine tumors are classified based on tumor differentiation and grade.²⁴ The incidence rate of neuroendocrine tumors metastasizing to the brain is approximately 1.5 to 5%, typically originating from the lungs.²⁵ In most cases, neuroendocrine tumors originate from the lungs, pancreas, or gastrointestinal tract. Metastases originating in the lungs are most likely to have single tumors in the brain, while primary neuroendocrine tumors of nonlung regions (i.e., esophagus, uterus, lymph nodes, or breast) will present with multiple brain tumors. One literature review of neuroendocrine tumors metastasizing to the brain recommended treatment with the gamma knife for three or less small tumors or cranial radiotherapy for a lesion with four or more tumors.²⁶

The unique histopathological findings required careful analysis to guide appropriate patient counseling and to determine next steps. This included a high Ki-67 index, which is unusual for this type of tumor. Ki-67 labeling index is a nuclear antigen that is present in cell cycle phases G1, S, G2, and M and is quantified by the antibody MIB-1.²⁷ In the 2004 WHO classification of endocrine tumors, PitNETs were classified as typical adenomas, atypical adenomas, and carcinomas. The definition of atypical adenomas included an elevated mitotic index, Ki-67 labeling index of greater than 3%, and nuclear staining for p53 immunoreactivity. Atypical adenomas also had features of invasive growth. However, subsequent studies found variability in the aggressive, invasive behavior of atypical adenomas, and the 2017 WHO classification system eliminated the definition of “atypical adenomas” and instead placed emphasis on high Ki-67 indices without a specific cutoff value because of the correlation of higher Ki-67 index with worse outcomes and a more aggressive treatment modality.^{19–21} The 2022 WHO classification of PitNETs takes Ki-67 labeling index into consideration but it is not the basis for tumor grading.²² In another study, a Ki-67 labeling index of greater than 1.5% is associated with a higher recurrence risk than disease-free survival time.²⁸ The correlation of the Ki-67 labeling index with tumor invasiveness, recurrence, and proliferation has varying significance among studies.^{27,29–31} This difference in findings might be attributed to the varying tumor behavior criteria of invasion and recurrence per study.^{21,32,33} Invasion and proliferation are independent phenomena of tumor behavior; however, these behaviors are often inappropriately combined in some studies, which further muddles the significance of

Ki-67 indices.^{29,34} Tumor invasion may be the strongest predictive factor of recurrence.^{31,33} Ki-67 labeling index is significantly correlated to growth of PitNETs, such as the one presented in this case. A Ki-67 labeling index of >1.5% was associated with a higher risk of rapid tumor regrowth.³¹ The Ki-67 index of 8% in this case was much higher than this threshold. Although this tumor presented invading into the surround neurovascular structures of the CPA, the Ki-67 index more likely reflects growth potential rather than invasive behavior of a PitNET.³¹ Despite variation in significance, the Ki-67 labeling index holds clinical relevance in predicting recurrence and thus should not be disregarded.²⁹

Kuroda et al reported a case in which a cerebellar neuroendocrine carcinoma that was initially suspected to be a cerebral metastasis mimicking hemangioblastoma in the right cerebellar region was found. Upon whole-body imaging, a primary lesion was not identified. Pathologic results were diffusely positive for CAM5.2 and pancytokeratin; positive for synaptophysin, CD56; weakly positive for CK5/6; and negative for glial fibrillary acidic protein (GFAP) and S-100. The Ki-67 labeling index was 62% in the lesion. Therefore, the most likely diagnosis is a neuroendocrine carcinoma metastatic tumor. Similar to the tumor presented in this case, this is a tumor with a high Ki-67 labeling index of neuroendocrine origin identified in the infratentorial region without evidence of a primary lesion. This tumor was treated with intensity-modulated radiotherapy (40 Gy in 20 fractions).³⁵

Ectopic pituitary tumors by definition present outside of the sella. Although ectopic pituitary tumors are rare, ectopic pituitary cells are rather common and found in the pharynx and leptomeninges of many healthy adults and fetuses.^{16,36} Thus, the hypothesis of improperly deposited pituitary cells during embryogenesis is unlikely due the nonpathological presence of ectopic pituitary cells. It is more likely that it is the neoplastic transformation of these ectopic cells that leads to tumorigenesis.¹⁶ Tanaka et al described a case in which a patient had an ectopic posterior pituitary identified inferior to the median eminence of the hypothalamus. The patient presented with transient headaches, and a CT scan revealed the absence of the infundibulum and neurohypophysis within the sella turcica. The patient did not have irregular adenohypophysis hormones and was also negative for diabetes insipidus. No treatment or intervention was performed.³⁷ Ortiz et al described an ectopic TSH-secreting PitNET within the sphenoid sinus. The patient presented with symptoms of primary hypothyroidism and was treated with levothyroxine for a year. The patient had high hormone levels and a left thyroid lesion upon investigation, and the hormone therapy was stopped. Central hyperthyroidism was suspected, and MRI revealed a sphenoid sinus mass with a physiologically normal pituitary gland. The ectopic TSH-secreting PitNET was confirmed with a suppression test with somatostatin. The ectopic tumor was removed with endoscopic transsphenoidal surgery, and the patient remained tumor-free at 2-year follow-up.¹⁴

Vernieri et al described a case in which a patient was diagnosed with a cerebellar well-differentiated neuroendocrine tumor found in the left cerebellar hemisphere with edema. Another plausible diagnosis for this case based on immunohistological staining was pineocytoma with mixed/intermediate differentiation; however, the absence of pineal localization and other specific markers lowered the likelihood of this diagnosis. Because this neuroendocrine tumor presenting in the cerebellum had not been described in the literature, a primary extracranial tumor was suspected. Despite a lengthy follow-up period, no extracranial lesion was identified, and the patient remained in remission until the recurrence of a cerebellar lesion 5 years later at the CPA.³⁸ Fainstein Day et al reported a case of an ectopic GH-releasing in the lung that metastasized to the left CPA. The metastasis caused displacement of the cerebellar fissure. The patient presented with skeletal changes of acromegaly and hearing loss in the left ear. The patient was treated with octreotide Long-acting release (LAR), which was exceedingly effective in relieving symptoms and reducing tumor size. Within 3 months, the serum level of GH normalized, and acromegaly symptoms diminished. With 18 months of treatment, the CPA tumor shrunk to 80% of its original size.³⁹

The first line of treatment for PitNET is most often surgical resection, excluding the treatment of prolactinomas, which are treated medically. Aggressive or recurrent PitNETs are treated with radiation therapy. Fractionated external beam radiation therapy (EBRT) and stereotactic radiosurgery (SRS) are also highly effective in pituitary tumor control. Side effects due to radiation injury must be weighed against benefits of therapy, with of course patient preference as paramount; however, the benefits often outweigh the risk in aggressive, high K_i -67 labeling index PitNETs.⁴⁰ A recent review article recommends surgery followed by SRS for PitNETs with a higher K_i -67 labeling index.⁴¹ The overall rate of serious complications following SRS is low due to precise tumor visualization in imaging studies for patient positioning.⁴¹ Fractionated conformal proton-beam therapy is also effective in controlling PitNETs.^{42,43} Proton therapy allows for maximal doses to deposit within the target tissue while eliminating the exit dose in surrounding tissue due to the larger size of the proton compared with the photon of radiation therapy.⁴³ The most common adverse effect of both SRS and proton therapy is hypopituitarism of which the rates were similar at the 3-year and 5-year follow-up. More data are needed to assess the long-term effects of proton therapy, but SRS has not been shown to have long-term toxicity.^{41,43}

In general, CPA tumors, usually vestibular schwannomas, are preferentially surgically treated as these are benign tumors presenting with symptoms secondary to mass effects rather than hormonal imbalances, paraneoplastic function, or invasive features.⁴⁴ However, the surgical approach is challenging and can be associated with postoperative headaches and cerebellar dysfunction. The retrosigmoid approach to dissecting CPA tumors has been modified to limit the need to retract the cerebellum for CPA access as well as improve reconstruction of the defect using only autologous bone.¹²

Takami et al reported a glioblastoma of the internal auditory canal, a rare tumor with only three case reports present in the literature, in which the surgical team initially suspected an early stage vestibular schwannoma. The patient presented with characteristic CPA tumor features, such as hearing loss and imbalance, but the symptoms rapidly progressed to facial weakness within 4 months. On MRI, the tumor had grown from 8 to 24 mm within that time frame. Due to the rapid growth of the tumor, the probability of malignancy increased. The surgical team surgically resected this tumor and followed with adjuvant chemotherapy and fractionated EBRT (total dose of 60 Gy). Although benign vestibular schwannomas are significantly more common, it is vital to maintain a level of suspicion to best treat the patient.⁴⁴

Conclusion

CPA tumors with characteristic internal acoustic meatus compression symptoms are most often vestibular schwannomas. PitNETs are typically present in the sella turcica. Ectopic PitNETs, though rare, have been described as originating in anterior skull regions, including the suprasellar region, sphenoid sinus, and clivus. Ectopic PitNETs within the CPA are extremely rare and a CPA tumor of neuroendocrine origin has only been described in literature once previously.³⁵ Our case illustrates the importance of considering unusual lesions such as ectopic PitNETs in unsuspecting locations if preoperative imaging exhibits unusual or invasive features, even if clinically nonfunctional. Surgical intervention is most commonly performed for the treatment of symptomatic PitNETs (excluding prolactinomas), tumors of the CPA (especially vestibular schwannomas), and ectopic PitNETs; however, radiation therapy can effectively be employed. It is important to have a detailed discussion with the patient about the risks and benefits of each treatment option to determine the next steps. In such cases of ectopic PitNETs, work-up to assess for metastasis is important. Our case is particularly noteworthy given the aggressive nature of this lesion and serves as a reminder to consider metastatic sources in such cases.

Ethics Approval

This study was performed in line with the ethical standards of the institution in which the study was conducted.

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Consent for Publication

The participant has consented to the submission of the case report to the journal.

Author Contributions

All authors approved the manuscript as it is written.

Conflict of Interest

None declared.

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